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GARNET – gene set analysis with exploration of annotation relations

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Abstract

Background: Gene set analysis is a powerful method of deducing biological meaning for an a priori defined set of genes. Numerous tools have been developed to test statistical enrichment or depletion in specific pathways or gene ontology (GO) terms. Major difficulties towards biological interpretation are integrating diverse types of annotation categories and exploring the relationships between annotation terms of similar information.

Results: GARNET (Gene Annotation Relationship NETwork Tools) is an integrative platform for gene set analysis with many novel features. It includes tools for retrieval of genes from annotation database, statistical analysis & visualization of annotation relationships, and managing gene sets. In an effort to allow access to a full spectrum of amassed biological knowledge, we have integrated a variety of annotation data that include the GO, domain, disease, drug, chromosomal location, and custom-defined annotations. Diverse types of molecular networks (pathways, transcription and microRNA regulations, protein-protein interaction) are also included. The pair-wise relationship between annotation gene sets was calculated using kappa statistics. GARNET consists of three modules - *gene set manager*, *gene set analysis* and *gene set retrieval*, which are tightly integrated to provide virtually automatic analysis for gene sets. A dedicated viewer for annotation network has been developed to facilitate exploration of the related annotations.

Conclusions: GARNET (gene annotation relationship network tools) is an integrative platform for diverse types of gene set analysis, where complex relationships among gene annotations can be easily explored with an intuitive network visualization tool (<http://garnet.isysbio.org/> or <http://ercsb.ewha.ac.kr/garnet/>).

Background

Omics studies usually yield a number of gene lists e.g. differentially expressed genes (DEGs). Typically, a statistical test of enrichment or depletion is performed for an a priori defined set of genes (usually from clustering of microarray data) or gene annotations. This approach has been successfully applied for diverse subjects including gene ontology (GO), signalling and metabolic pathways, and identification of regulatory elements such as transcription factors and microRNAs. However, biological

interpretation of gene lists is still a challenge for many biologists because there is no 'golden standard method' established yet. Numerous annotation DBs and tools have been developed for biological interpretation of experimental gene lists including but not limited to GSEA [1], DAVID [2], Gazer [3], FatiGO+ [4], g:Profiler [5], WebGestalt [6] Lists2Networks [7] and GOAL [8]. A comprehensive list of 68 GSA web tools is recently reviewed by Huang *et al* [9] as well as several important points to consider in using such tools. As Huang and colleagues suggests, each tool has its own strength and limitations in terms of statistical method, coverage of gene annotation types and user interface [9].

One important issue in the field is the growing complexity of annotation data themselves. The benefit of

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gene set analysis (GSA) mainly comes from the power to summarize hundreds or even thousands of genes into a smaller number of enriched biological themes e.g. GO term or pathways, allowing simplified interpretation of high-throughput experiments. However, the analytic complexity of GSA is getting beyond its benefits because of the rapid increase of gene annotations e.g. a few dozens of genes can be enriched in a hundred or more annotation terms. The number of GO terms is already more than the number of genes in a human genome and the situation is getting similar with other types of annotation like pathways, the regulatory targets of TFs and miRNA, disease-associated genes and chromosomal locations even without considering their combinations [10]. Increasingly, omics data continue to be sources of new annotations e.g. cancer signature genes from microarray [11] and disease-associated genes from GWAS studies [12]. Major difficulties towards meaningful biological interpretation are integrating diverse types of annotations and at the same time, handling the complexities for efficient exploration of annotation relationships.

GARNET (Gene Annotation Relationship Network Tools) is an integrative platform for diverse types of gene set analysis, allowing convenient annotation network navigation. The utility of GARNET is two-fold. One is to facilitate the interpretation of gene sets from high-throughput experiments such as microarray, ChIP-chip (ChIP-Seq) and high-throughput screening. The other is to serve as a framework for meta-analysis of heterogeneous annotations and pre-existing knowledge, which often lead to novel insights undetectable by individual analyses [13]. In an effort to allow access to a full spectrum of amassed biological knowledge, we have integrated a variety of annotation data that include the GO, domain, disease, drug, chromosomal location, and custom-defined annotations. Diverse types of molecular networks (pathways, transcription and microRNA regulations) are also included. To deal with the complexity from a large number of annotations from different categories, a dedicated annotation network viewer has been developed for the visualization of related annotations.

GARNET system consists of three modules – *gene set retrieval tool*, *gene set manager tool*, and *gene set analysis tool*, which are tightly integrated to allow access, manipulation and statistical analysis of pre-compiled gene annotations and user-defined gene lists. The relationship between annotation terms is calculated using Cohen's kappa statistic. Kappa is less sensitive to the gene set size than other P-value statistics such as Chi-square, hypergeometric and binomial test because it measures the difference between the observed and the expected agreement between two annotation terms.

Construction and content

System overview

Considering highly exploratory nature of gene set analysis, GARNET is designed to navigate different layers of gene annotations in a convenient and integrated environment, equipped with ID conversion module, an interactive network viewer and import/export of any gene sets. GARNET contains four major groups of gene annotation information – molecular network, gene function, gene expression, and disease & drugs (Figure 1a). Molecular network data include pathways, protein-protein interactions, and microRNA targets from several different sources. We also included gene annotation data such as gene ontology, protein domain and chromosomal location as well as differentially expressed genes (DEGs) from gene expression data. Gene-disease and gene-drug associations are also compiled from relevant sources [14]. Further, any user-defined gene annotation data can be uploaded and analyzed against all the annotations in the system. The detailed scope of annotation data is provided in Table 1 and on-line.

The GARNET system consists of three main tools – manager, analysis, and retrieval tools. Figure 1(b) shows the workflow of GARNET analysis. Users define gene sets using the manager tool where the set operation is available to combine two gene sets as union, intersection, and subtraction. The analysis tool performs enrichment test for the user-supplied genes in the annotation categories of choice. Multiple test correction is applied by default since there are so many annotation terms. The result of statistical analysis is given in table format where one can access the network view of annotation terms. In addition to the flat table view, GARNET also supports the tree view for hierarchical annotations such as GO and OMIM disease terms. The retrieval tool allows users to access the annotation database to extract genes assigned to any annotation term. Importantly, users may expand their gene list using the molecular networks in the annotation database. This novel feature allows users to investigate the down-stream effects of their genes of interest.

Any gene set analysis requires an ID system. We chose the Entrez geneID as the reference ID system instead of devising our own. This alleviates the maintenance (update & expansion) problem significantly since most annotation databases provide the cross-reference to the Entrez geneID. GARNET supports most major gene IDs including Entrez Gene ID, Ensembl Ids (Gene, Transcript), GenBank, RefSeq, UniProt and microarray probe IDs (Affymatrix, Illumina). The detailed list of supported ID types is listed in Table 2. Even though we support diverse ID types for input, all subsequent

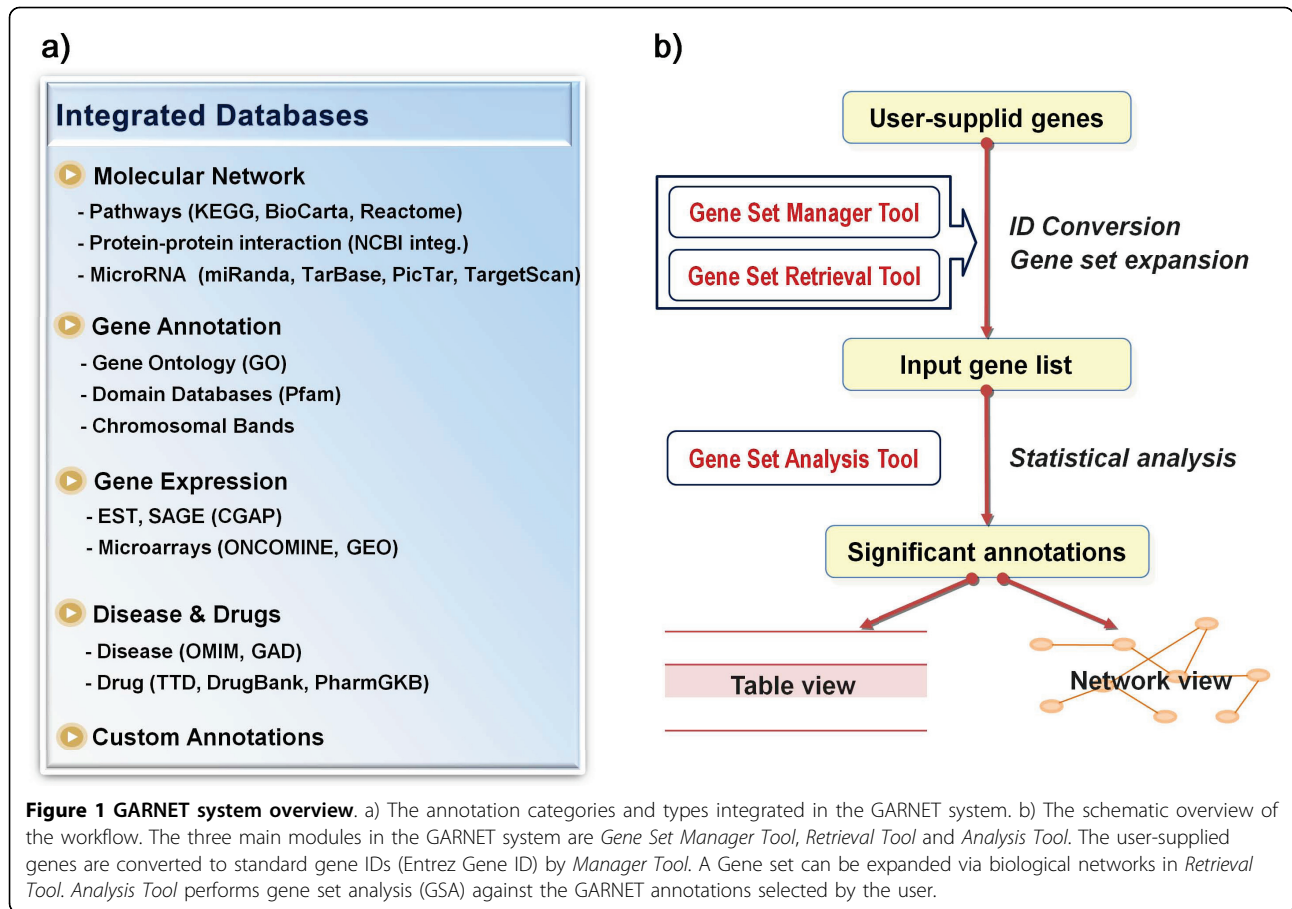


Table 1 Summary of the annotation categories and types in the GARNET system

Category	Annotation DB	Number of Annotations	Number of Unique Genes	Version	Update Date
Molecular Network	KEGG	199	5193	Release 54.0+/-	2010.05.10
	BioCarta	314	1383		2010.04.06
	Protein-Protein Interactions (PPI)	5829	7631	NCBI integrated DB	2010.05.17
	miRBase	711	34525	5.0	2009.09.29
	TarBase	106	394	V5	2008.06
	TargetScan	162	7930	4.2	
	PicTar-4way	178	9152	hg17, Build 35	
	PicTar-5way	130	3455	hg17, Build 35	
Genome Annotation	Gene Ontology (GO)	30479	18242		2010.05.20
	Pfam domains	3922	16409	24.0	2009.10.07
	Chromosomal Bands	3078	32920		2010.05.23
Gene Expression	Tissue EST	51	13367		2010.04.06
	Tissue SAGE	32	8528		2010.04.06
	Tissue Microarray	32	10769		
	Cancer Microarray	25	13619		
Disease & Drug	OMIM	1063	2683		2008.08.27
	GAD	1212	2872		2008.12.26
	DrugBank	591	259		
Total		57973	32920		

Table 2 List of supported ID types in GARNET

Category	ID Type	Examples
Gene ID	Entrez Gene	1457, 2002, 1950
	Ensembl Gene	ENSG00000101266
	Ensembl Transcript	ENST00000361797
	GenBank Accession	AB451279, A1628974
	GenBank ID	19769225, 4665774
	RefSeq	NM_130786, NM_000014
	UniGene	Hs.41, Hs.56
Protein ID	HGNC Gene Symbol	A1BG, A1CF, A2LD1
	HGNC Gene ID	7, 8, 7645
	UniProtKB Accession	P62258, Q04917
	UniProtKB ID	1433B_HUMAN
Microarray	PIR Accession	S34755, A61235, I38947
	Affymetrix probe ID	212073_at, 210984_x_at
	Illumina probe ID	4210086, 2510484

analyses are carried out at the gene level, not protein or transcript level.

Datasets

A comprehensive set of gene annotation data are integrated in the GARNET system (Table 1). The annotations

are grouped into four different categories of molecular network, genome annotation, gene expression, and disease & drug. The molecular network category consists of pathways (KEGG [15], BioCarta), protein-protein interactions (PPI) from NCBI and four major miRNA target databases (miRBase [16], TarBase [17], TargetScan [18] and PicTar [19]). The category of genome annotation contains information on gene function (Gene Ontology [20]), protein domain (Pfam [21]) and chromosomal location. Tissue-specific or cancer-related gene expression data are included in the gene expression category. We also collected gene-disease (OMIM [22], GAD [12]) and gene-drug association (DrugBank [14]) data from relevant sources, that are deposited in the disease & drug category.

User interface

Manager Tool

The gene set manager tool (*Manager Tool*) is the main entry point to access all the annotation data and further gene set analysis in GARNET. The overall workflow is shown in Figure 2. In *Manager Tool*, user may create or delete a new gene set by either entering a list of gene IDs or uploading an input file. The input gene IDs are automatically converted to Entrez Gene IDs. All the

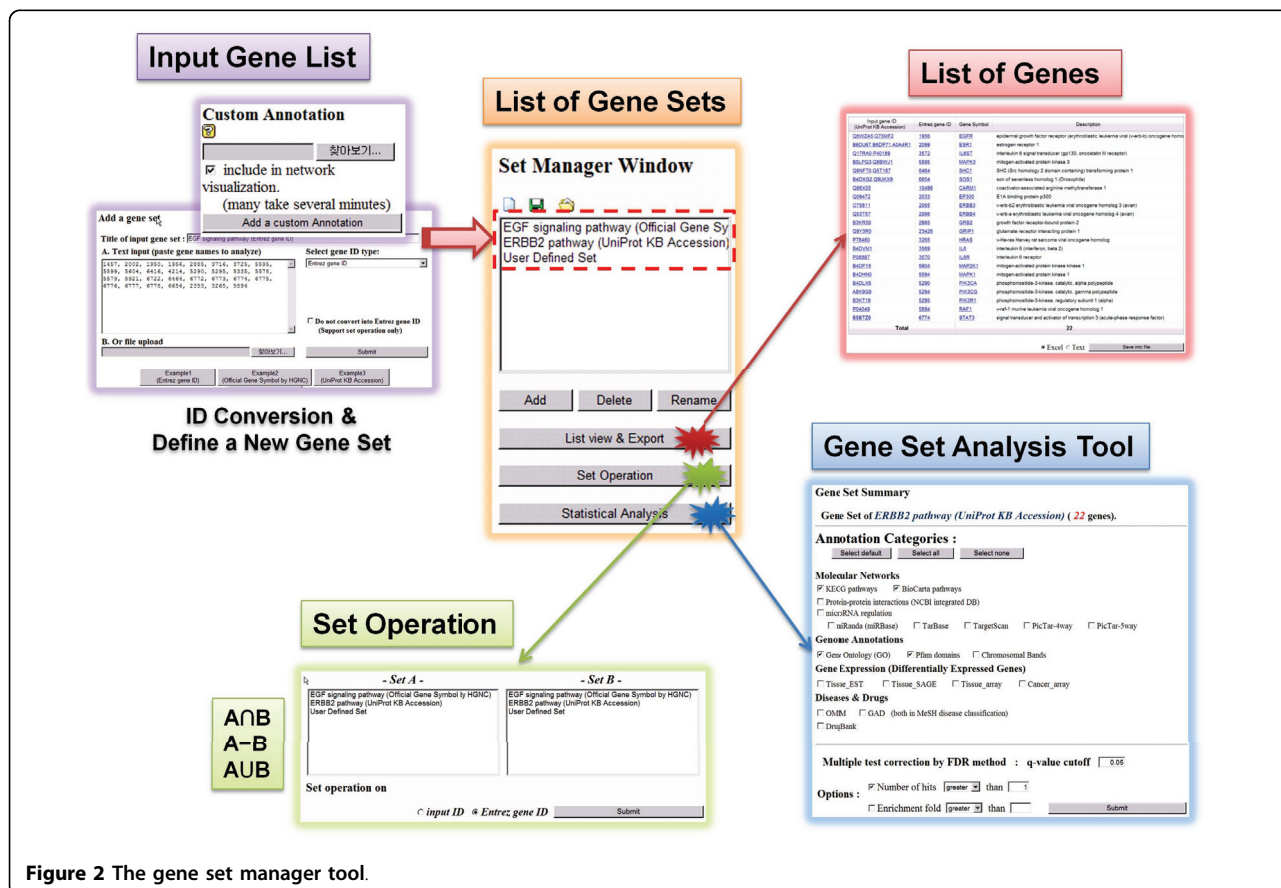


Figure 2 The gene set manager tool.

user-created gene sets are listed up in a separate panel named *Set Manager Window* (dotted red box in Figure 2), where the gene set of interest can be chosen. Users can access the member genes of the chosen gene set or create a new gene set by set operation of existing gene sets e.g. interaction, subtraction, and union. Once gene sets are prepared in the *Manager Tool*, user can proceed to *Analysis Tool* for gene set analysis or *Retrieval Tool* for expanding gene list along the biological networks as described in the later sections.

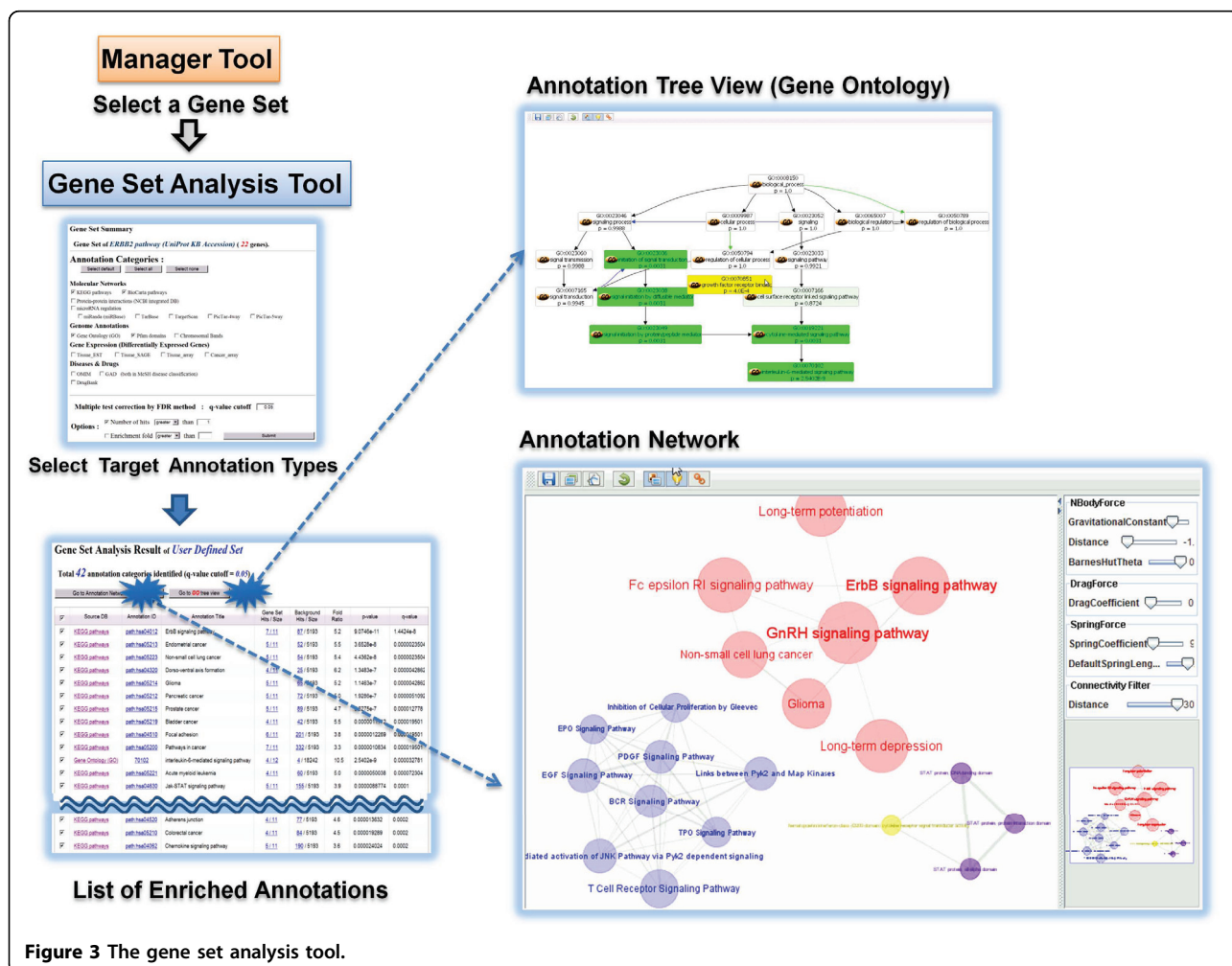
Analysis Tool

Analysis Tool implements the core function of statistical over-representation analysis against various types of gene annotations. User selects a target gene set and can perform GSA against multiple types of annotations simultaneously. The overall procedure of GSA is shown in Figure 3. Kappa statistic is used as the enrichment score in GARNET. Multiple test correction is done by Benjamini-Hochberg method. The stringency of GSA is set as $q\text{-value} < 0.05$ by default, but the $q\text{-value}$ cut-off

can be adjusted according to the user's preference as well as by the number of hit annotations. As a result of GSA, the list of significantly enriched annotations is displayed as table view. Particularly, the relationships among the enriched annotations are presented in an interactive network viewer. The annotation network data are downloadable in standard formats for other visualization tools (e.g. cytoscape) or network clustering softwares (e.g. MCL [23]) for further analysis. It also opens the chance to reveal connections among heterogeneous types of annotations e.g. miRNA targets and cancer signature genes, drug targets and protein. Annotations such as Gene Ontology and MeSH terms have hierarchical structure, which is displayed in tree view as well (top-left in Figure 3).

Retrieval Tool

Retrieval Tool is for getting the member gene list of existing annotations and for expanding the existing gene sets via various types of biological networks. For example, miRNA target genes can be expanded via



transcriptional regulatory network, and then by PPI network and so on (Figure 4). Gene set expansion via networks can be useful in combination with set operations e.g. intersection and difference in the *Manager Tool*, allowing a great freedom to navigate and combine the different aspects of existing knowledge. All the gene sets in GARNET is accessible by keyword or ID search and the member genes are listed in the resulting page (Figure 5).

Conclusions

GARNET (gene annotation relationship network tools) is an integrative platform for diverse types of gene set analysis, where complex relationships among gene annotations can be easily explored with an intuitive network visualization tool.

Availability and requirements

GARNET is available at <http://garnet.isysbio.org/> and <http://ercsb.ewha.ac.kr/garnet/>.

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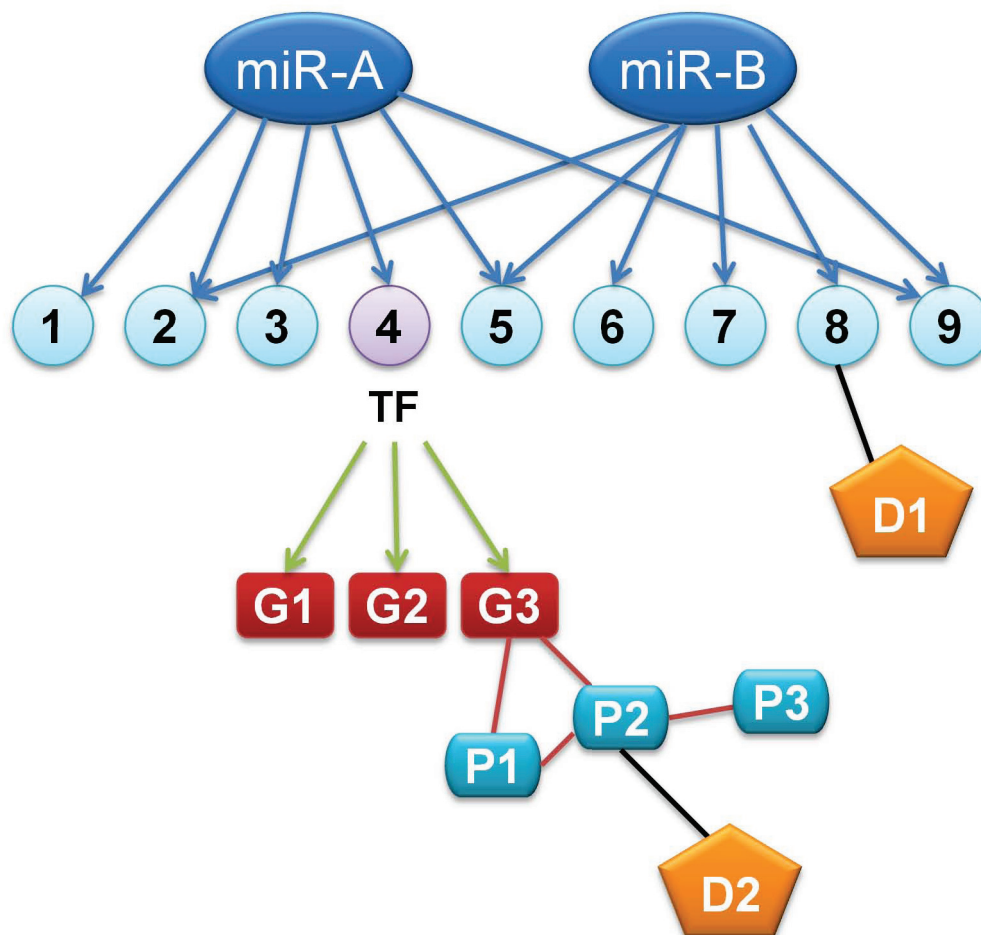


Figure 4 An example of gene set expansion via various types of biological networks. The targets of two microRNAs (miR-A and miR-B) can be expanded by transcription factor (TF)-target network (green edge) to include G1~G3. The gene set is further expanded via protein-protein interaction network (red edge) to include P1~P3. D1~P2 and D2~8 represents Drug-target relationship (black edge).

Part A. Search the gene network

Title of input gene set :
Gene Set #001

Text input
(paste gene names to analyze)

Select gene ID type:
Affy Probe ID

Example1 (Entrez gene ID) | Example2 (Official Gene Symbol by HGNC) | Example3 (microRNA)

Expand by molecular networks :

- Pathway (KEGG, BioCarta)
- Transcriptional regulation (TRANSFAC)
- Protein-protein interactions (NCBI integrated DB)
- microRNA regulation
 - miRanda (miRBase)
 - miRanda (miRBase) Show miRNA list
 - TarBase
 - TargetScan
 - PicTar-4way
 - PicTar-5way

Options : up-stream down-stream both

expansion : 1 (Maximum : 5 steps)
 (The 1-step expansion means the nearest neighbor only)

Note that protein-protein interaction is independent of direction selection.

Part B. Search the annotation terms

Title of input gene set :
Gene Set #001

Annotation terms / nodes : [Clear all]

Pathways
 "KEGG" : path:hsa03320, path:hsa04010, ...
 "BioCarta" : h_cytokinePathway, h_stressPathway, ...

Gene Ontology
GO:000

Pfam Domain
PF0138

Disease
OMIM D002386, ...

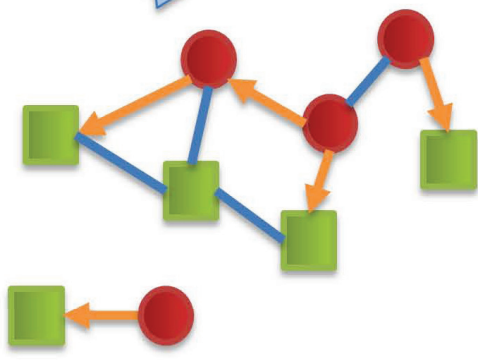
Drug
APRD00264, APRD00085, ...

Data type : [None] Tissue : [None]

Diff. Expression
 up down both

Chromosomal band
16p11.2 (or 16 or 16p or 16p11)

Expand Gene Set by Network



Output Gene List

Total 33 genes. Add into the gene set manager

<input type="checkbox"/>	Entrez gene ID	Gene Symbol	Description
<input checked="" type="checkbox"/>	23746	ABPL1	aryl hydrocarbon receptor interacting protein-like 1
<input checked="" type="checkbox"/>	493862	ABCC1	Age-related cortical cataract 1
<input checked="" type="checkbox"/>	7439	BEST1	bestrophin 1
<input checked="" type="checkbox"/>	8119	BFS2P2	beaded filament structural protein 2, plakinin
<input checked="" type="checkbox"/>	8130	CATM	cataract, congenital, with microphthalmia
<input checked="" type="checkbox"/>	878	CGA1	cataract, congenital, cataract type, 1
<input checked="" type="checkbox"/>	269979	COX6P	Cataract, congenital, nuclear progressive
<input checked="" type="checkbox"/>	1410	CRYAB	crystallin, alpha B
<input checked="" type="checkbox"/>	1411	CRYBA1	crystallin, beta A1
<input checked="" type="checkbox"/>	1414	CRYBB1	crystallin, beta B1
<input checked="" type="checkbox"/>	1415	CRYBB2	crystallin, beta B2
<input checked="" type="checkbox"/>	1417	CRYBB3	crystallin, beta B3
<input checked="" type="checkbox"/>	1420	CRYGC	crystallin, gamma C
<input checked="" type="checkbox"/>	1421	CRYGD	crystallin, gamma D
<input checked="" type="checkbox"/>	1422	CRYGS	crystallin, gamma S
<input checked="" type="checkbox"/>	10306	CTPP	Cataract, posterior polar
<input checked="" type="checkbox"/>	1769	DMPK	dystrophia myotonica-protein kinase
<input checked="" type="checkbox"/>	2138	EVA1	eyes absent homolog 1 (Drosophila)
<input checked="" type="checkbox"/>	2512	FTL	ferritin, light polypeptide
<input checked="" type="checkbox"/>	2584	GALK1	galactokinase 1
<input checked="" type="checkbox"/>	2592	GALT	galactose-1-phosphate uridylyltransferase
<input checked="" type="checkbox"/>	2651	GCHT2	glucosaminyl (N-acetyl) transferase 2, I-branched enzyme (I blood g
<input checked="" type="checkbox"/>	2208	GJA3	gap junction protein, alpha 3, 46kDa
<input checked="" type="checkbox"/>	2203	GJA8	gap junction protein, alpha 8, 50kDa
<input checked="" type="checkbox"/>	3299	HSE4	heat shock transcription factor 4
<input checked="" type="checkbox"/>	3459	IFNGR1	interferon gamma receptor 1
<input checked="" type="checkbox"/>	3596	IL13	interleukin 13
<input checked="" type="checkbox"/>	619404	LOC619404	cataract, congenital nuclear, autosomal recessive
<input checked="" type="checkbox"/>	4284	MIP	major intrinsic protein of lens fiber
<input checked="" type="checkbox"/>	80207	OPA1	optic atrophy 3 (autosomal recessive, with chorea and spastic parap
<input checked="" type="checkbox"/>	5309	PITX3	paired-like homeodomain 3
<input checked="" type="checkbox"/>	4990	SIX6	SIX homeobox 6
<input checked="" type="checkbox"/>	6652	SORD	sorbitol dehydrogenase
Total			0

Figure 5 The gene set retrieval tool.

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Competing interests

The authors do not have any competing interests.

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